REMARKS

The Amendments

Independent Claims 130 and 151 are amended to recite testosterone undecanoate as the androgen. They are also amended to eliminate the recitation regarding extent of effectiveness, since this statement was alleged in the Office Action to be non-distinguishing. The claims dependent thereon are amended accordingly. Independent claim 162 is amended to recite an intramuscular mode of administration, administration also of an androgen and to recite that the interval time is at least 6 weeks. The dependent claims are amended accordingly and a new dependent claim fully supported by the disclosure is added. Also, new claim 187 derives from original claim 162 reciting non-oral administration and that the androgen is testosterone undecanoate.

To the extent that the amendments avoid the prior art or for other reasons related to patentability, competitors are warned that the amendments are not intended to and do not limit the scope of equivalents which may be asserted on subject matter outside the literal scope of any patented claims but not anticipated or rendered obvious by the prior art or otherwise unpatentable to applicants. Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

The Rejection under 35 U.S.C. § 103

The rejection of the claims under 35 U.S.C. § 103, as being obvious over Guerin (Intnl. J. Andrology) is respectfully traversed.

The discussion of Guerin in the Reply with RCE Filing of June 6, 2003, still applies and is incorporated herein by reference. Guerin teaches, as its contribution, three specific regimens for daily administration of hormones for male contraception. In all three regimens,

the progestagen (e.g., norethisterone acetate) is administered orally. Guerin also discusses what was allegedly done before their contribution in the section entitled "Introduction" at the first and second pages. It is alleged in the Office Action that this latter section of Guerin teaches that "both steroid classes [progestagens and androgens] are generally administered by intramuscular injections," citing the following paragraph of Guerin:

> "In the past 15 years, several clinical studies have been published concerning combination treatment with progestagens, mainly medroxyprogesterone acetate (MPA) and androgens, mainly testosterone enanthate (TE). Both steroid classes are generally administered by intramuscular injections, with high initial doses followed by maintenance doses injected monthly or biweekly (Coutinho & Melo, 1973, Alvarez-Sanchez et al., 1977, Schearer et al., 1978, Faundes et al., 1981 and Frick et al., 1982)." (Emphasis added)

Guerin, thus, relies on five articles for this allegation. But Guerin provides an incorrect reading of these articles and one of ordinary skill in the art reading Guerin and being knowledgeable of the prior art, including these articles, would know that it is incorrect. Instead, one of ordinary skill in the art would have known from these articles that intramuscular injections are only mentioned in connection with regimens combining medroxyprogesterone acetate (MPA) and testosterone enanthate. With respect to all other progestagens used, only oral administration (or means other than intramuscular injection) is suggested. Copies of the five articles are provided herewith and they can be summarized as follows.

Coutinho and Melo, 1973 (Contraception 8, pp. 207-217) describe implants comprising testosterone and either norgestrione or norethindrone, optionally in combination with orally administered progestagens. There is no intramuscular injection.

Alvarez-Sanchez et al, 1979 (Int J Androl, 2, pp. 136-149) describe monthly injections of medroxyprogesterone acetate and testosterone enanthate and conclude that this treatment schedule is not adequate for contraceptive purposes (see abstract).

Schearer et al, 1978 (International J Andrology, suppl 2, pp. 680-709) describes the following regimens:

- orally administered megestrol acetate combined with T implants (Table 3, panels 1 and 2).
- orally administered norethindrone, optionally in combination with T implants (Table 4, panels 1 and 2).
- orally administered norethanandrolone, optionally in combination with T implants (Table 5, panels 1 and 2).
- orally administered d-norgestrel, optionally in combination with T implants (Table 6, panels 1 and 2).
- orally administered d-norgestrione in combination with T implants (Table 7, panels 1 and 2).
- orally administered R2323 in combination with T implants (Table 8, panels 1 and 2).
- Intramuscular injection of Depo-medroxyprogesterone acetate in combination with T implants or monthly intramuscular injection of testosterone enanthate in (Table 9, panels 1 and 2).

Of the 7 different types of regimens described by Schearer et al 1978, only one regimen relates to the intramuscular injection of a progestagen, namely Depo-medroxyprogesterone acetate, and an androgen, namely testosterone enanthate. The authors conclude "that none of the regimens reviewed here appear suitable for further development as a male contraceptive" (1st paragraph, column 2, page 709). It is further mentioned that "in view of the strong demand for a pharmacological contraceptive product for men, this possibility merits the attention of continued research and development efforts, including screening studies to identify progestins and androgens that possess high potency in suppressing spermatogenesis" (last paragraph, column 2, page 709).

Faundes et al, 1981 (Int J Andrology, 4, pp. 235-245) relate to monthly injections of medroxyprogesterone acetate and testosterone enanthate. The authors conclude that "combination of DMPA/TE has a powerful inhibitory effect over spermatogenesis, but the monthly schedule tried by us does not offer real promise of becoming a practical contraceptive for men, within a dose range free of potential toxicological effects. Perhaps other forms of administration can still be tried" (3rd paragraph, page 244).

Frick et al, 1982 relates to biweekly or monthly injections of medroxyprogesterone acetate and testosterone enanthate for providing male contraception. It is said that biweekly administration schedule was chosen, based on the hope to maintain a full inhibitory effect on the spermatogenesis and thereby azoospermia in all subjects. Restoration of spermatogenesis nevertheless occurred in a few subjects of both groups of treatment. The authors conclude that the treatment protocols (biweekly or monthly injections) proposed are inadequate for long term male contraception.

Thus, a full reading of Guerin with the supporting articles cited therein does not provide a suggestion regarding injection of the entire classes of steroids in general for male contraception. Guerin's review of these articles is incorrect and that would be evident to one of ordinary skill in the art. Accordingly, it is urged that Guerin, considered as a whole by one of ordinary skill in the art, does not teach or suggest compositions or kits comprising an effective amount of a norethisterone derivative and testosterone undecanoate in non-oral administration form. See amended claims 130, 151 and 187. Also, it does not teach or suggest intramuscular injection of both a norethisterone derivative and an androgen; see amended claim 162. The intramuscular injection teachings of the art are limited to the MPA and testosterone enanthate combination.

Furthermore, Guerin does not teach contraceptive efficacy with biweekly or monthly injections of hormones. It teaches only daily administration. According to each of the

Alvarez-Sanchez, Schearer, Faundes and Frick articles, the intramuscular injection of medroxyprogesterone acetate (MPA) and testosterone enanthate is not adequate for male contraceptive purposes. It is particularly stated by Alvarez-Sanchez that monthly injection intervals or biweekly injections are not suitable for male contraceptive purposes. See abstract and last paragraph of in the paper of Alvarez-Sanchez. Thus, Guerin, as a whole considering the cited article teachings, also does not motivate the skilled person to provide administration schemes involving long-term intervals between non-oral (e.g., intramuscular) injections for the purpose of providing effective male contraception. Particularly, there is no suggestion of methods for providing male contraception by administering one particular group of progestagens, namely norethisterone derivatives, and an androgen, in intervals of at least 6 weeks, as recited in independent claims 162 and 187.

The discussion of the Kamischke article in the Reply filed with RCE Filing is incorporated herein by reference and the following additional comments are provided for emphasis. The article shows that, upon selecting norethisterone derivatives as the progestagenic compound in male contraceptive regimens and selecting long-term intervals between non-oral administration, significant suppression of sperm count in all participants occurs (page 532, col. 1, third paragraph). In the conclusive remarks on page 537-538 of Kamischke, it is stated that the "efficacy in all groups of the combination of TU (testosterone undecanoate) and norethisterone (norethisterone enanthate) has proven better than in nearly all other previous studies for hormonal male contraception." Kamischke indicates that most potential users of male contraception would prefer an injection-independent application of the hormones, but except for the combination of norethisterone acetate with transdermal testosterone in a gel formulation, the injection or implantation-free approaches have failed so far to suppress spermatogenesis sufficiently (page 534, column 2, paragraph 1). This indication corresponds with the failure of the regimens investigated in the articles cited in

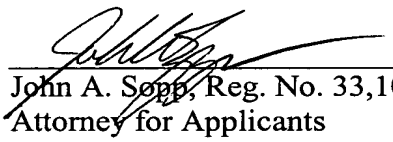
Guerin (see the review of these articles above). Thus, this showing of unexpected advantages and patentability of the instant claims is even more probative and convincing than previously discussed because the failure of the prior art methods is recognized in the articles relied on by Guerin and the instant composition and kit claims are now more closely tailored to the showing provided here (i.e., more commensurate in scope with the instant claims). The showing of unexpected advantages in the Kamischke article is clear and convincing evidence of the nonobviousness of the claimed invention.

For all of the above reasons, it is urged that Guerin, considered as a whole, fails to render the claimed invention obvious to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. § 103 should be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



John A. Sopp, Reg. No. 33,103
Attorney for Applicants

MILLEN, WHITE, ZELANO &
BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: PLOVIN-3A

Date: February 5, 2004

JAS/slm:K:\plovin\3a\Reply to 9-5-03 OA.doc